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EFFECTS OF CENTRAL NERVOUS SYSTEM
IRRADIATION ON HUMAN PERFORMANCE,
BLOOD PRESSURE AND EMOTIONAL STATE

Aaron Wolfgang, et al

Walter Reed General Hospital

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BLOOD PRESSURE AND EMOTIONAL STATE**

HEADQUARTERS
Defense Nuclear Agency
Washington, D.C. 20305



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13. ABSTRACT <p>The overall aim of this study was to assess changes in human performance as a result of various combinations of dose, time, and volume of central nervous system irradiation. Twenty-eight separate behavioral measures ranging from blood pressure, motor coordination, and muscle strength, to memory, motivation, anxiety, and decision-making ability were obtained.</p> <p>Overall, the results showed that relatively young healthy subjects receiving central nervous system irradiation involving the spinal cord or brain for extra-cranial neoplasms showed no performance decrement when compared to the matched controls on a broad range of behavioral functions. Even the extreme cases receiving the highest dose and volume of ionizing irradiation showed no apparent performance decrement. The only objective measure that was significant was blood pressure where a decline was found particularly in diastolic blood pressure from the pre-exposure to post-treatment trials. However, the blood pressure changes although statistically significant were not large enough to be clinically significant.</p>		

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**The experimental work with volunteer human subjects discussed
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III
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TABLE OF CONTENTS

	<u>Page</u>
Introduction - - - - -	1
Background information to the problem - - - - -	2
Methodology - - - - -	3
Description of subjects - - - - -	3
Procedure - - - - -	3
Description of behavioral measures, <u>Ss</u> task and apparatus - - - - -	5
Results - - - - -	11
Cases with the highest dose and greatest volume of CNS irradiation - - - - -	21
Discussion - - - - -	27
References - - - - -	33
Distribution list - - - - -	35

LIST OF ILLUSTRATIONS

<u>Figure</u>		<u>Page</u>
1	Mean seconds to respond of brain, spinal and nonirradiated controls for pre-exposure and last radiation treatment -----	14
2	Mean diastolic blood pressure of brain, spinal and nonirradiated controls over five trials -----	17
3	Mean anxiety scores over four trials -----	19

V

LIST OF TABLES

<u>Table</u>		<u>Page</u>
1	Biographical data of radiated subjects -----	4
2	Description of tests and measures -----	6
3	Means and standard deviations of pre-, final, and post- exposure for brain radiated, spinal radiated, and controls--	12

VI

INTRODUCTION

This is the final report of the project entitled "Effects of Central Nervous System (CNS) Irradiation on Human Performance, Food Pressure and Emotional State." Data collection has been completed, the results analysed, and a complete report of the findings follows.

The authors are grateful for the assistance of Juanita Weaver, Pat Coakley, and Dan Hoeschen in data collection and analysis and to Major Robert Quillin, the radiobiological physicist who computed the tumor doses in Rets to the brain and spinal cord. Lastly, the most appreciation of all is expressed to the patients who graciously cooperated throughout the project under the most trying circumstances.

BACKGROUND INFORMATION TO THE PROBLEM

We live in a nuclear age where increasing numbers of individuals are being exposed to radiation from a variety of sources (e.g., nuclear reactors, atomic fallout, nuclear waste, and medical X-rays used for treatment and diagnosis). Yet at present a great deal more is known about effects of radiation on behavioral changes in animals than humans. It is generally agreed that there have been pitifully few systematic studies reported in the Western literature on this subject (Furchtgott, 1963; Kimeldorf and Hunt, 1965).

How much impairment can be expected to such vital human functions as memory, motor coordination, muscle strength, blood pressure, and decision making ability when the central nervous system has been irradiated at various combinations of dose, time, and volume? The overall aim of this research is to attempt to find the answers to some of these largely unanswered questions.

Human studies on this subject can be characterized as being mainly descriptive, stemming from radiation accidents (e.g., Frisby, 1961) or atomic bomb casualties from World War II. However, it was impossible to determine if any performance decrement could be attributed to radiation since measures of pre-exposure levels of functioning were absent. In one study where pre- and post-radiation measures were obtained, the results showed that ionizing irradiation given in whole-body or partial-body doses did not adversely affect psychomotor or cognitive performance (Payne, 1963), (Saenger, Friedman, Horowitz, Kerelakes, 1967-68). However, since terminal cancer patients in their advancing years participated and such variables as age, education, motivation and IQ were not controlled, it was impossible to separate the effects of these variables from radiation effects.

METHODOLOGY

Description of Subjects.

A total of 24 subjects (Ss) from Walter Reed General Hospital participated in the study. The 16 Ss who were receiving radiation treatment were selected by the radiotherapist for evaluation in accordance with the following criteria: Under 50 years of age, minimum of ninth grade education, no brain damage, and no psychoses. Only patients categorized as clinical Stage I or State II of the neoplastic disease participated. This means that the patients' tumors were localized and amenable to radiation treatment. The eight control Ss were employees of Walter Reed Hospital.

The 24 Ss were divided into three groups with eight Ss in each group. One group was called the brain irradiated group, this group was treated for tumors of the scalp or face (e.g., lymphoma of the scalp) with the brain being in the field of radiation. Another group was called the spinal irradiated group which only had the spinal cord in the field of radiation (e.g., testicular seminoma). The control group was called the nonirradiated group and received no radiation treatment. The three groups were matched for sex, age, and education. There was a total of nine females and 15 males in the sample. The overall average age and education of the three groups was 30 years and 14 years, respectively. The vocabulary portion of the Shipley-Hartford (SH) Test of Intelligence was administered, and an analysis of variance on the raw scores showed that there were no significant differences between the groups ($P > .05$). A resume' of the radiation cases is in table 1.

Note in table 1 the tumor dose in Rets and dose to the brain and spinal cord were calculated by the following formula: $\text{Total Dose} = \text{NSD} \times N^{0.24} \times T^{0.11}$ where NSD is the Nominal Single Dose, N is the Number of Fractions, and T is Total Time. The NSD is expressed as Ret or Rad equivalent Therapeutic (Ellis, 1968).

Procedure.

Prior to evaluation, the radiotherapist in charge of treating the patients explained to the patients that they would be given a battery of tests supervised by

TABLE 1.--Biographical data of radiated subjects

Case	Sex	Age (yrs.)	Education (yrs.)	Diagnoses	Radiation Source	Tumor Dose Rets	Estimated Tumor Dose to Brain in Rets (Depth 2 cm. Below Scalp) and Spinal Cord (5cm. Depth from Posterior Skin Surface).
*I	F	23	15	Suspected Medulloblastoma	60 Co	983	983
II	M	45	12	Lymphoma of Scalp	300kV	1,351	1,102 (Dose Taken at 5 cm. Depth)
III	M	22	15	Carcinoma Left Paranasal Sinuses	2mV p	1,891	1,891
IV	F	27	12	Lymphoepithelium Nasopharynx	60 Co	1,677	1,677
V	M	22	12	Lymphoepithelium Nasopharynx, Left	60 Co	1,758	1,758
VI	F	37	12	Adenocarcinoma Rt. Max. Atrum	60 Co	1,869	1,869
VII	M	50	16	Basal Cell Carcinoma	140kV	1,567	783 (Dose Taken at 4 cm. Depth)
VIII	M	41	17	Metastatic Seminoma to Skull	60 Co	1,076	960 (Dose Taken at 4 cm. Depth)
**IX	F	23	16	Hodgkins Disease	2mV p	Field:	Dose at midline and End of treatment:
X	M	37	12	Testicular Seminoma	60 Co	Mediastinum	1,106
XI	M	24	19	Teratocarcinoma Stage II	60 Co	Peri-aortic	1,293
XII	F	41	15	Hodgkins Disease Stage 1A	2mV p	Mediastinum	1,202
XIII	F	27	15	Carcinoma of Right Breast	60 Co	Peri-aortic	843
XIV	M	19	12	Teratocarcinoma Rt. Testicle	60 Co	Mediastinum	1,385
XV	M	23	16	Hodgkins Disease Stage 11A	60 Co	Peri-aortic	1,385
XVI	M	25	11	Seminoma	60 Co	Mediastinum	1,803 (Dose at end of Treatment)
						Mediastinum	619
						Mediastinum	953
						Peri-aortic	1,412
						Mediastinum	1,274
						Cervical-Axilla	412
						Cervical-Axilla	634
						Peri-aortic	1,138
						Mediastinum	1,172

*Brain irradiated group (I-VIII)

**Spinal irradiated group (IX-XVI)

a psychologist in the Behavioral Science Lab. The Lab was located in the Radiotherapy Service, a short distance from the treatment area. It was explained to the patient that the testing was another phase of treatment, the evaluation phase. The arrangement between the psychologist and the Chief of Radiotherapy was that if when evaluating the patient there was any unusual performance decrements shown on the tests after radiation, the radiotherapist would be immediately informed.

Upon completion of treatment the patient went to the Behavioral Science Lab where the testing procedures were explained. The patients were evaluated with a battery of tests on five separate occasions as follows:*

- (a) pre-exposure or sham irradiation where the patient was set up as if to be treated but instead a diagnostic radiograph of the field to be irradiated was taken. Thus, in this condition a baseline measure was taken
- (b) at the first treatment
- (c) at the middle of the series of treatments
- (d) after the last radiation treatment, and
- (e) a post-treatment measure; i. e., a 1-month follow-up.

One patient was unavailable for the 1-month follow-up and was evaluated after 3 months. The average time between testing sessions was computed for the irradiated subjects, and it was at these times that the nonirradiated control group was tested. The Ss were cooperative, and all completed the tests.

Description of Behavioral Measures, Ss Task and Apparatus.

A total of 28 separate measures were obtained over each of five or two trials for each subject (S). These measures can be classified into distinct categories representing different behavioral functions as shown in table 2. A more detailed description of the tasks and apparatus is described below.

(A) Efficiency in Decision Making (Concept Identification (CI)).

An automated Visual-Tactile CI System was developed to objectively measure efficiency in categorizing information presented either visually or tactually. The Ss task was to correctly categorize a series of stimuli (geometric figures).

*On some tests only two forms were available, and they were given at pre-exposure and after the last treatment.

TABLE 2.--Description of tests and measures

Name of Test	Measures Used	No. of Times Administered
<u>Concept Identification</u>		
Visual	Number of errors to solution	5
Tactile	Number of errors to solution	5
Visual latency	Number of seconds to respond	5
Tactile latency	Number of seconds to respond	5
<u>Intelligence</u>		
Shipley (verbal)	Number of correct items	2
<u>Memory</u>		
Digit span	Number of digits recalled - forward and backward	5
Memory for design (forms A and B)	Points for accuracy in drawing designs	2
Immediate and Delayed Paired Associate Learning	Number of correct associations	2
<u>Motor Coordination</u>		
Tapping with dominant and nondominant hand	Tapping speed - Average number of taps per 10 seconds over three trials	5
Perdue Pegboard with dominant, nondominant, and both hands	Total number of pins inserted at end of 30 seconds	5
<u>Muscle Strength</u>		
Dynamometer with dominant and nondominant hand	Kilograms	5
<u>Cardio-Vascular Changes</u>		
Systolic blood pressure	Average millimeters of pressure over two trials	5
Diastolic blood pressure	Average millimeters of pressure over two trials	5
<u>Motivation</u>		
Effort on test	Five-point scale from "tried as hard as I could" to "not at all"	5
Liking for test	Five-point scale from "liked the test very much" to "not at all"	5
<u>Emotional State</u>		
Anxiety level in test situation	Raw score	5
Depression in test situation	Raw score	5
Hostility	Raw score	5
Anxiety, depression and hostility in general	Raw scores	2

TABLE 2. --Description of tests and measures (Continued)

Name of Test	Measures Used	No. of Times Administered
<u>Time Horizon</u>	Check one of eight time categories from "Can't see into the future at all" to "Can see beyond <u>5</u> years or more into the future"	2
<u>Social Distance</u>	Millimeters ^a	2
<u>Health Questionnaire</u>	Three-point scale from poorer, to worse or less than, to more than usual	5

The presentation of the stimuli and duration of feedback was automated. Ss' errors and latency of response was printed out on a printout counter. It was possible to control the complexity of the task by varying the proportion of relevant to irrelevant information. The more irrelevant information there was, the more complex the task. To reduce the possibility of practice effects, the solution to each problem was changed, and in each problem one new bit of irrelevant information was added. Thus, there were five CI problems presented visually and two tactile problems. It has been shown (Burn, 1967) that Ss with Central Nervous System (CNS) damage perform significantly poorer on a CI task than their respective controls. A more detailed description of the task and apparatus is described in an earlier publication (Wolfgang, 1971a).

(B) Intelligence Measures. The verbal portion of the SH test was divided into two forms. One form represented the odd items and the other even. The correlation between the two forms was $r = .85$. The SH test has been shown to be a rapid and accurate intellectual screening instrument (Prado and Cannon, 1965).

(C) Memory. Portions of the Wechsler Memory Scale Form I and II were administered as follows: (1) Digit Span Forward and Backward, (2) Memory for Designs, and (3) Paired Associate Learning. The Digit Span Test was expanded from two forms to five by creating numbers on each new form by using the table of random numbers. The Memory for Designs Test requires the Ss to draw from memory simple geometric figures exposed for 10 seconds. The Memory for Designs was also administered again 45 minutes later to assess both immediate and delayed memory. Traditionally, memory tests tap only immediate memory and don't answer the question of how long information can be stored and retrieved. In the Paired-Associate Learning Test, the Ss were read a list of words two at a time; then only one word was presented, and the S was expected to fill in the correct association. If the Ss failed, they were told the correct word, and the list was repeated a total of three times in a different order each time.

(D) Motor Coordination. The Halstead finger-tapping test and the Perdue Peg-board Test were used as sensorimotor measures. Total testing time for both tests was only 8 minutes. Both tests have shown to be of value in detecting CNS dysfunction (Vega, 1969). On the finger-tapping test, the number of taps per 10-second period was tallied by a counter for only three consecutive trials

instead of the usual five, because in pilot testing Ss showed no difference in performance from trial three to trial five. On the Perdue Pegboard Test, Ss tried to place as many pins as they could in a row within a 30-second period. To determine the dominant hand, Ss were asked what hand they wrote and threw a ball with and then were asked to touch the tip of their nose. If they said they used the right hand, then the right hand was considered dominant.

(E) Muscle Strength. A hand dynamometer was used as an index of general bodily strength. Ss were allowed three trials with each hand, right and left alternately. Ss were encouraged to squeeze the dynamometer as hard as they could. This test can also be used as an index for motivation. The average score for the three trials on each hand was tallied.

(F) Cardiovascular Changes.

Blood Pressure (BP)--Before the readings were determined, Ss were seated in a comfortable chair and asked to relax. Ss were in a sitting position with their left arm resting on a table, and then two measures of systolic and diastolic BP were obtained with the standard aeronoid cuff type sphygmomanometer and averaged.

(G) Motivation. Motivation, particularly in radiation research, is an important variable that needs to be assessed when considering the possibilities of radiation causing general weakness or fatigue. Two aspects of motivation were evaluated as follows on a five-point scale: (1) Effort expended on the test where Ss checked one of the categories which ranged from "tried hard as I could" to "tried not at all", and (2) Liking for the tests ranging from "liked the test very much" to "not at all."

(H) Emotional State.

To measure degree of anxiety in each testing session the Multiple Affect Adjective Check List (MAACL) was used (Zuckerman and Lubin, 1965). Two forms of the test were used, the "General" and "Today" forms. The items in both tests were the same, but the instructions were different; i. e., the Ss had to check words describing how they "generally" felt or in terms of how they felt "now" or "today."

The MAACL gives measures of three emotional states; i. e., anxiety, depression, and hostility, and has been recommended for use in taking repeated

measurements of affect over time. The anxiety scale in particular has been shown to be a sensitive measure of reactions to stressful situations (Zuckerman, *et al.*, 1965). The "Today" form was administered before each testing session and the "General" form at the first interview and the last radiation treatment.

(I) Health Questionnaire. The health questionnaire was administered orally to each S at each testing session. The aim of the questionnaire was to determine if radiation affected Ss on the following categories: sleep, eating, drinking, headaches, vision, hearing, and nausea. Ss were asked if they were affected, less than usual, as usual or more than usual. If Ss said less or more than usual, they were asked to explain. For vision and hearing, Ss were asked if it was better, as usual, or poorer.

(J) Time Horizon. To determine how far into the future Ss could see what their life would be like, they were asked to check one of eight time categories ranging from "cannot see into the future at all" to "can see beyond 5 years into the future." This test was used primarily to determine if Ss would plan for the future; have hope for the future beyond the time of radiation treatment and their illness. This test was administered prior to treatment and at the end of the final treatment.

(K) Social Distance Test. This test was used to determine how Ss who have received radiation treatment versus Ss who have not would react or feel about approaching an individual accidentally exposed to radiation. That is, would they keep their distance or offer help? The results and a description of the test are described in an earlier paper (Wolfgang, 1971b) on file at DNA.

RESULTS

The main statistical technique used for analyzing the data was analysis of variance repeated measures. In addition, correlational analyses were performed on the data. Table 3 gives an overall summary of the results showing the means and standard deviations of Ss at the pre-, final and post-exposure levels.

(A) Performance in Cognitive Functioning.

1. Conceptual or Decision Making Ability. The results showed that there were no significant differences in error-rates across trials or between the groups in solving visual or tactile CI problems ($P > .05$). However, overall brain ($\bar{X} = 7.05$) and spinal irradiated Ss (7.23) tended to make fewer errors than the controls ($\bar{X} = 12.48$).

The results relating to speed (sec.) of decision making on the visual CI task showed no significant differences ($P > .05$) either between the three groups or across trials. However, the control groups tended to take less time in making decisions than the irradiated Ss, across all trials.

An analysis of latency of decisions on tactile CI showed that there were significant differences between the three groups ($F = 4.40$, $df = 21$, $P < .05$); across trials ($F = 53.23$, $df = 21$, $P < .001$) and on the interaction between groups and trials ($F = 49.01$, $df = 21$, $P < .001$). Both the spinal ($\bar{X} = 3.83$ sec.) and control groups ($\bar{X} = 3.00$ sec.) took less time to make a decision than the brain irradiated group ($\bar{X} = 5.24$). However, as figure 1 shows, the differences between the groups were due primarily to differences at the pre-exposure level of radiation. At the final exposure level, there were no significant differences between the groups ($P > .05$). It can also be seen in figure 1 that all three groups improved their performance over the pre-exposure level, thereby making it doubtful that it was radiation that facilitated the brain irradiated Ss performance.

It was noted that on the tactile task Ss decision time ($\bar{X} = 4.01$ sec.) was twice as long as on the visual task ($\bar{X} = 2.13$ sec.). This finding was consistent with a previous study using a similar task and apparatus (Wolfgang, 1971a). Since Ss normally learn to make decisions using primarily the visual senses to make decisions rather than tactile, it is not surprising that it would take longer to classify information using only the tactile sense.

TABLE 3.--Means and standard deviations of pre-, final, and post-exposure for brain radiated, spinal radiated, and controls

		Pre-Exposure		Final Exposure		Post-Exposure	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
<u>Conceptual Ability</u>							
Visual Error	Brain	8.13	5.94	8.50	15.27	7.38	12.85
	Spinal	11.25	16.45	3.25	1.83	5.75	7.03
	Control	12.38	16.01	5.50	9.59	20.38	17.83
Tactile Error	Brain	7.25	8.00	2.00	1.60		
	Spinal	6.88	10.02	1.75	1.16		
	Control	8.00	7.93	7.25	10.40		
Visual Latency (sec.)	Brain	2.95	1.76	2.78	1.39	2.60	2.09
	Spinal	1.78	1.33	2.18	1.55	2.85	1.69
	Control	1.64	1.04	1.53	.78	1.66	.99
Tactile Latency (sec.)	Brain	7.34	3.25	3.14	1.45		
	Spinal	4.94	1.23	2.72	1.49		
	Control	3.52	1.42	2.50	1.32		
<u>Intelligence</u>							
Shipley (Verbal)	Brain	32.25	5.06	30.50	3.96		
	Spinal	30.75	7.48	28.25	4.95		
	Control	30.25	7.67	28.00	5.86		
<u>Memory</u>							
Digit Span	Brain	7.25	.71	7.25	.89	7.63	.52
	Spinal	6.63	.74	6.63	1.06	7.00	.93
	Control	6.63	1.41	6.63	1.30	6.63	1.06
Memory for Design	Brain	11.38	2.20	12.00	2.88		
	Spinal	11.13	3.31	12.00	2.45		
	Control	12.25	2.60	13.38	2.50		
Paired Associate Learning	Brain	25.00	3.51	24.38	4.72		
	Spinal	22.50	4.11	22.25	6.27		
	Control	23.75	6.07	23.25	6.34		
<u>Motor Coordination</u>							
Tapping (Dominant)*	Brain	45.18	5.20	49.60	5.33	50.43	5.15
	Spinal	46.98	5.22	49.99	3.30	48.38	3.23
	Control	48.95	4.59	50.38	4.93	50.06	6.62
Perdue Pegboard (Dominant)	Brain	13.62	1.85	15.75	1.49	15.38	1.92
	Spinal	15.13	1.96	16.00	1.51	16.13	1.25
	Control	15.88	2.13	16.88	1.46	16.13	1.25

*There is a significant difference between the overall means of male and female Ss.
Overall mean of males = 50.78, overall mean of females = 45.75.

TABLE 3.--Means and standard deviations of pre-, final, and post- exposure for brain radiated, spinal radiated, and controls (Continued)

		Pre-Exposure		Final Exposure		Post-Exposure	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
<u>Muscle Strength</u>							
Dynamometer (Dominant Hand) *	Brain	43.21	9.56	45.74	12.09	46.05	10.04
	Spinal	44.46	11.15	46.83	13.67	47.25	12.11
	Control	47.37	14.07	46.86	12.13	47.84	11.82
<u>Cardio-Vascular Changes</u>							
Systolic	Brain	110.00	7.29	105.25	10.22	104.91	7.76
	Spinal	109.75	6.36	103.88	5.59	99.69	3.84
	Control	107.50	10.36	106.50	7.78	103.75	8.65
Diastolic	Brain	71.75	4.06	66.13	11.68	64.38	8.55
	Spinal	62.56	7.17	62.13	3.91	61.06	3.01
	Control	66.63	6.82	68.19	5.24	67.63	5.42
<u>Motivation</u>							
Effort on Test**	Brain	4.13	.99	4.38	.74	4.25	.89
	Spinal	4.13	1.46	4.00	1.41	3.75	1.39
	Control	4.00	.93	3.75	1.28	4.13	.99
Liking for Test***	Brain	3.75	.71	4.13	.64	4.13	.64
	Spinal	4.25	.46	4.13	.35	4.13	.35
	Control	4.25	.46	4.13	.64	4.25	.46
<u>Emotional State</u>							
Anxiety Level in Test Situation	Brain	5.63	3.70	3.63	3.63	4.50	4.87
	Spinal	6.25	2.92	4.75	2.71	5.25	2.82
	Control	7.13	4.32	5.63	5.17	8.50	5.13
Depression in Test Situation	Brain	9.25	5.90	7.50	6.39	8.50	9.23
	Spinal	10.25	5.97	10.63	6.95	9.38	6.63
	Control	12.25	6.11	14.63	8.16	13.75	7.15

* There is a significant difference between the mean of male Ss and female Ss. The overall mean of males = 54.00, the overall mean of females = 32.98.

** Effort on Test 5 = as hard as I could.

4 = very hard.

3 = fairly hard.

*** Liking for Test 5 = very much.

4 = pretty much.

3 = little.

TACTILE LATENCY

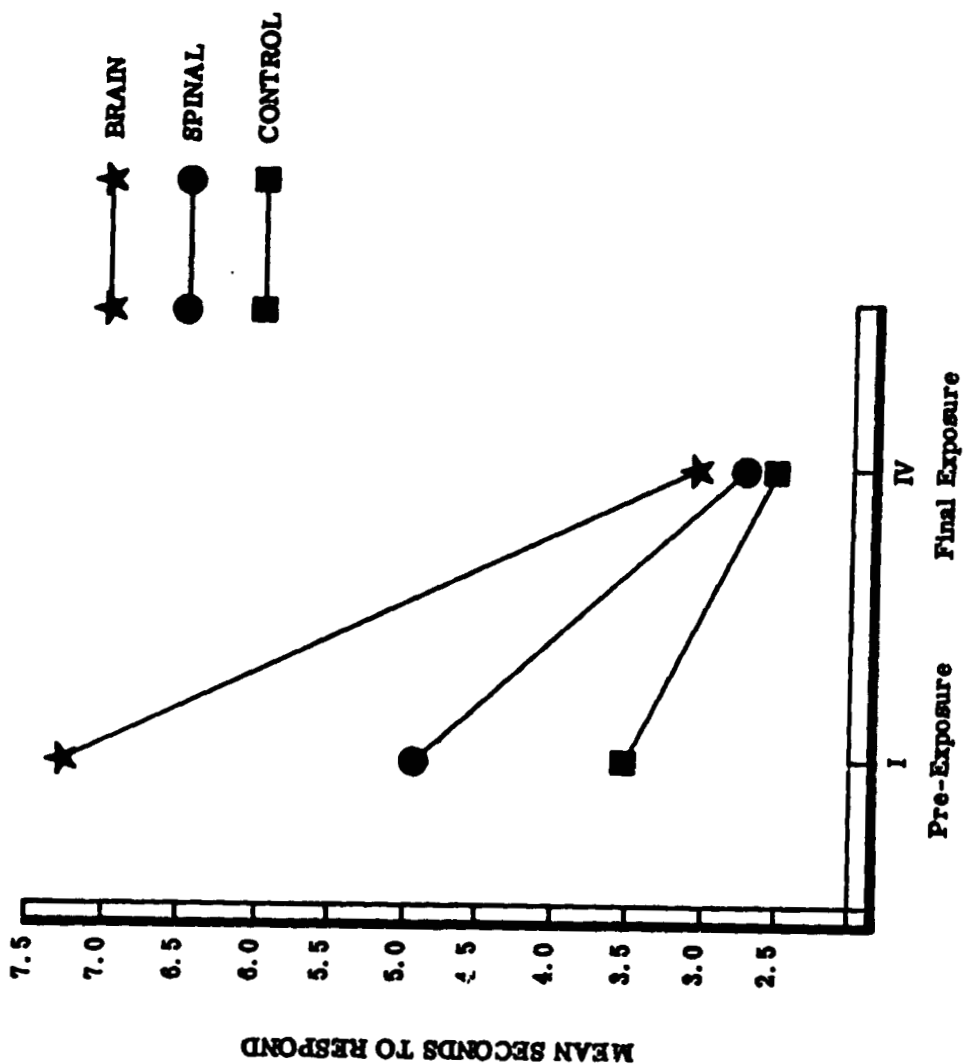


Figure 1. --Mean seconds to respond of brain, spinal and nonirradiated controls for pre-exposure and last radiation treatment.

2. Memory Performance. In memorizing digits forward or backward, there were no significant results to report ($P > .05$). Overall, the memory span for repeating a series of numbers forward was seven and backward six. The brain irradiated Ss scores were slightly higher across all trials for digits forward or backward.

On the memory for designs test, on immediate recall (10 sec.) or delayed (45 min.), there were no significant results ($P > .05$). A perfect score is 14, and on immediate recall the overall average score was 12.02, and on delayed recall 11.46.

On the paired-associate learning task where Ss had to learn to remember words that go together (i. e., Baby--Cries or Obey--Inch), there were no significant differences in the results. Brain irradiated Ss tended to earn higher scores across all trials than spinal or control groups (see table 3).

(B) Motor Coordination.

On the tapping test with the dominant and nondominant hands, the only significant results were that Ss showed significant improvement across trials with the dominant hand ($P < .01$). The average tapping speed in a 10-second period for the brain irradiated Ss was ($\bar{x} = 48.67$), for spinal ($\bar{x} = 48.53$), and for the control nonirradiated Ss ($\bar{x} = 49.94$). A significant sex difference was found for tapping speed on the dominant hand ($P < .001$) with the males tapping significantly faster ($\bar{x} = 50.78$) than females ($\bar{x} = 45.75$). Overall tapping speed on the dominant hand was faster ($\bar{x} = 49.04$) than on the nondominant hand ($\bar{x} = 44.53$).

On the Perdue Pegboard, which is a test of manual dexterity, the Ss were tested with the dominant, nondominant, and both hands, and the only significant results were across trials where Ss showed improvement with the dominant ($P < .01$) and nondominant hands ($P < .05$) and slight improvement when performing with both hands ($P < .10$). The overall mean scores for the brain, spinal, and nonirradiated controls were 15.13, 15.17, and 16.40 respectively, with the controls showing a slightly higher performance level across all trials than the brain irradiated Ss.

(C) Muscle Strength. An analysis for muscle strength (kg.) was performed on the hand dynamometer for the dominant and nondominant hands. The results showed that for the dominant hand there were no significant results in muscle

strength ($P > .05$), whereas in the nondominant hand Ss overall performance decreased over trials ($P < .01$). There was also a significant interaction on the nondominant hand between trials and groups ($P < .05$) indicating that the spinal irradiated Ss showed lower muscle strength scores over all radiation exposure times than brain irradiated Ss and controls, but in the follow-up they performed similarly to the controls and brain irradiated Ss. As anticipated, there were significant differences in muscle strength between male ($\bar{x} = 54$ kg.) and female Ss ($\bar{x} = 32.98$ kg.).

(D) Cardiovascular Changes.

1. **Systolic Blood Pressure.** The only result that showed significance was across trials ($P < .01$); i.e., Systolic BP showed a progressive decline over five trials. The biggest overall drop in BP was between the pre-exposure trial ($\bar{x} = 109$) and the post-exposure trial ($\bar{x} = 103$), a decrease of 6mm.

2. **Diastolic Blood Pressure.** The analysis showed that there were significant interaction effects between groups and trials ($F = 32.48$, $df = 84$, $P < .001$) and across five trials ($F = 23.68$, $df = 84$, $P < .001$). The trials effect indicated that diastolic BP showed an overall decline from trial one to five. Thus, the results of both diastolic and systolic BP were similar in that they both indicated an overall drop in BP from the baseline. However, in taking a closer look at the data by viewing the interaction in figure 2 between groups and trials, it was the brain irradiated group that showed the sharpest decline in diastolic BP, while the other groups showed slight or no change from the baseline. The biggest change in BP in the brain irradiated group was from the baseline (pre-exposure) to follow-up averaging 8 mm.

(E) Motivation. An analysis on the motivation scores showed no significant results on the two measures: One indicating effort, and the other liking for the tests. On a five-point scale from one to five, Ss averaged four indicating they worked "very hard" on the tests, and for degree of liking the tests Ss average score was four, the four-category indicated the Ss like the tests "pretty much." Overall, the results suggest that Ss were motivated to perform well on the tests, and that all three groups (brain, spinal, and nonirradiated controls) showed similar motivation levels.

BLOOD PRESSURE, DIASTOLIC

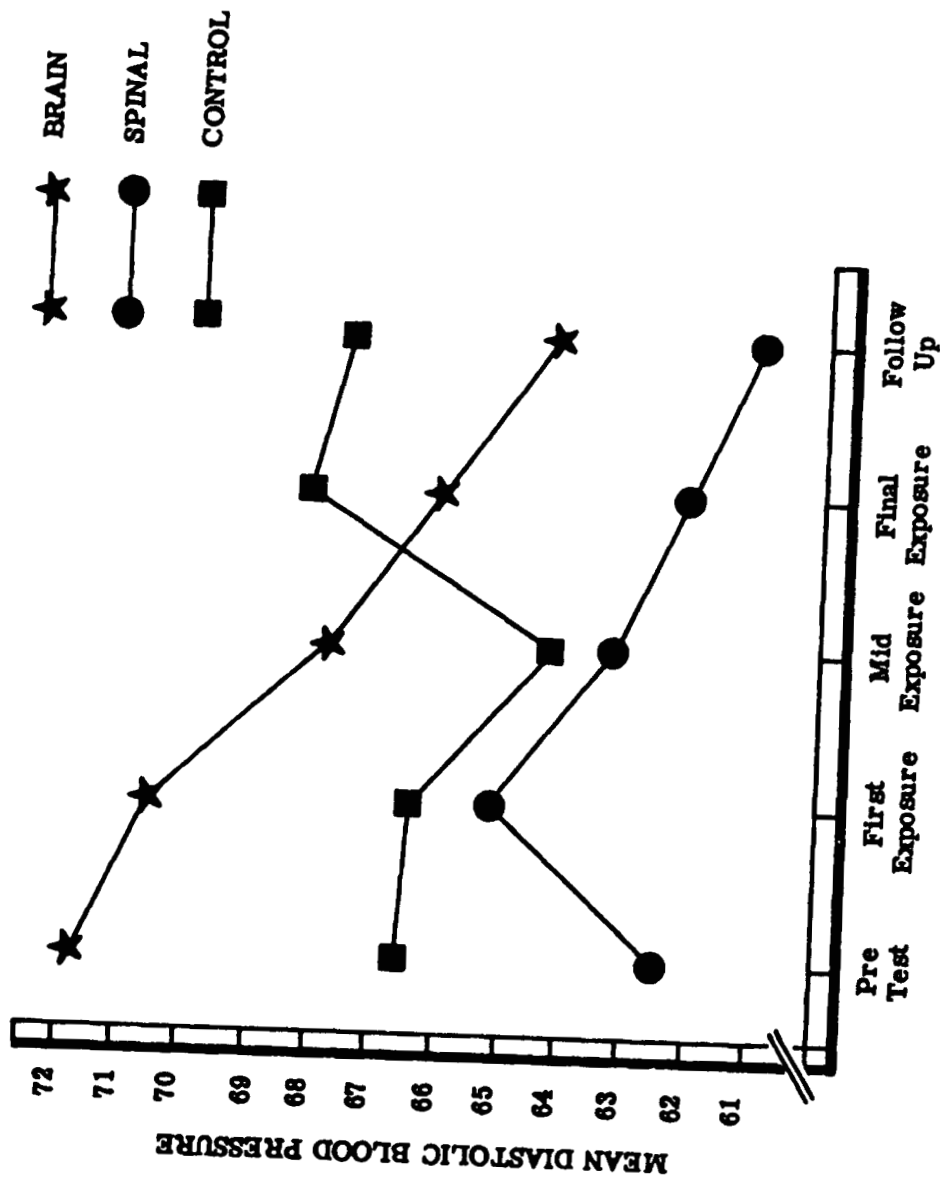


Figure 2. ---Mean diastolic blood pressure of brain, spinal and nonirradiated controls over five trials.

(F) Emotional State.

An analysis of the anxiety scores in the test situation (Today form) showed that the interaction between groups and trials was significant ($F = 3.63$, $df = 84$, $P < .01$). As figure 3 shows, brain irradiated Ss showed the least amount of anxiety across all trials and showed a gradual drop in anxiety with radiation treatment from the pre-exposure to the post-exposure trials. The overall mean anxiety scores for the brain irradiated Ss were 4.38, spinal 6.55, and 7.43 for nonirradiated Ss.

On the depression scale of the MAACL, the brain irradiated Ss test scores showed the least amount of depression across all trials and were significantly different from the controls ($P < .05$) on all trials except on the pre-exposure trial, where there were no differences ($P > .05$). The overall average depression scores for the brain irradiated Ss were 8.43, for spinal 11.23, and 13.60 for the nonirradiated controls.

In analyzing the results on the hostility scale of the MAACL, the brain irradiated Ss reported having significantly less feelings of hostility than the controls ($P < .05$). Mean hostility scores for the brain, spinal, and nonirradiated Ss were 4.85, 6.2, and 8.48, respectively. The brain irradiated Ss reported the least amount of hostility across all trials than the controls or spinal irradiated Ss, and the spinal irradiated Ss hostility scores were consistently lower than the controls. Thus, overall, the results suggest that the brain irradiated Ss were the least anxious, depressed, and hostile, and the controls the most, with the spinal irradiated scores in between.

(G) Time Horizon. When Ss were asked how far into the future they could clearly see what their life would be like, the analysis of the time scores showed no significant differences between the groups ($P > .05$). On the whole, the Ss could see 1 year into the future, which indicates a degree of optimism and hope about the future, even though two-thirds of the Ss were being treated with radiation for a life threatening disease. These measures were taken at the pre-exposure level and when the final treatment was completed.

(H) Health Questionnaire.

To evaluate to what degree radiation affected Ss general health, a health questionnaire was administered orally by the experimenter after each radiation

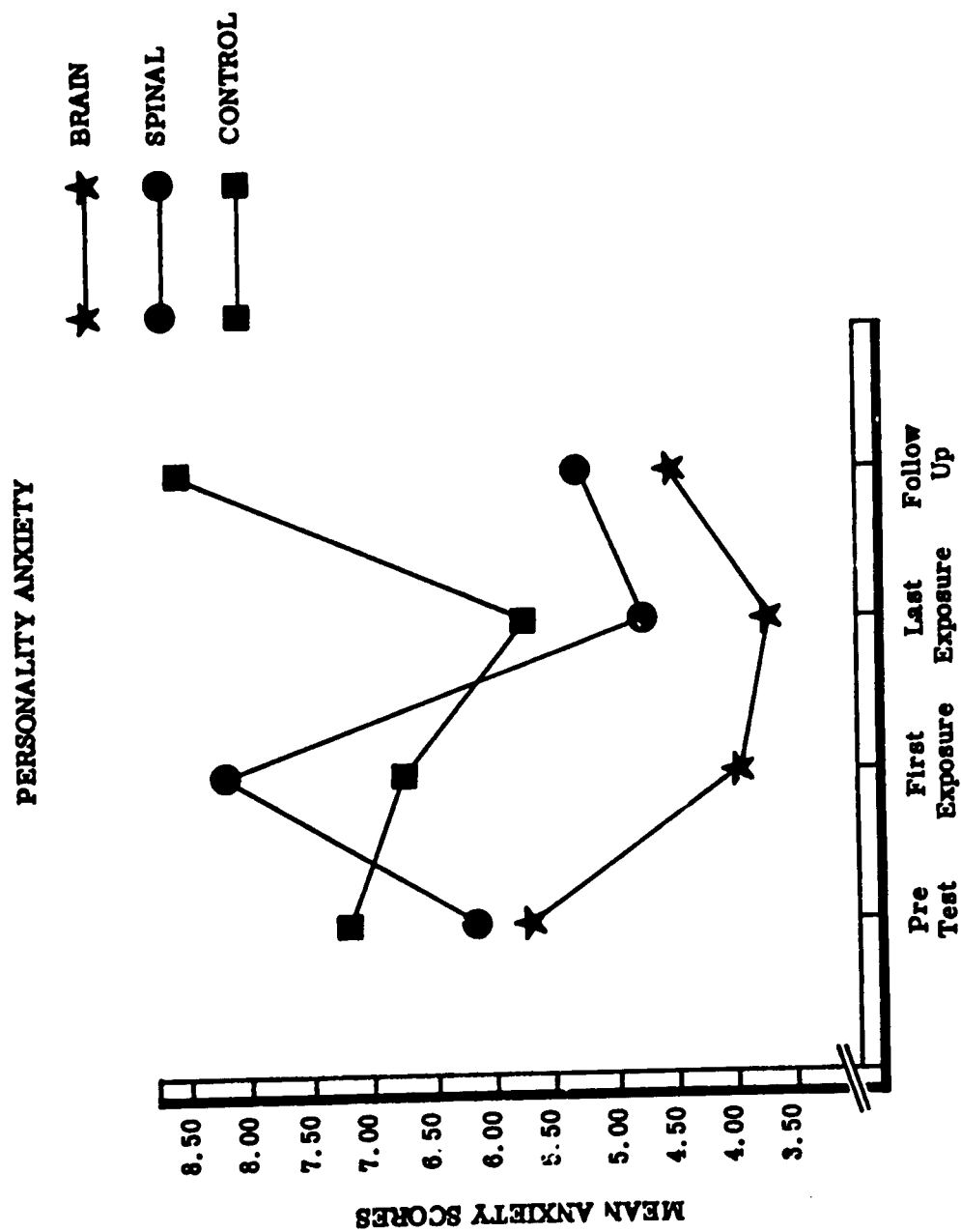


Figure 3. -- Mean anxiety scores over four trials.

treatment and follow-up after 1 month. Changes in Ss frequency of eating, sleeping, drinking, headaches, and nausea were evaluated along a three-point scale: Affected less than usual, as usual, and more than usual. The same procedure was used for assessing changes in vision and hearing except the categories poorer, no change, and better than usual were used. The frequency of responses in each category was tallied across five trials from pre-exposure to 1-month follow-up. The results showed that in the nonirradiated group only 10 percent of the responses deviated from the normal health pattern, compared to 33 percent for spinal irradiated Ss, and 18 percent for brain irradiated Ss. The two areas where spinal irradiated Ss reported the greatest frequency of complaints were for headaches and nausea.

About half-way through the total number of days of radiation treatment (3rd trial), spinal irradiated Ss showed the greatest frequency of complaining of nausea; with seven out of eight patients reporting feeling more nauseous than usual. However, Ss were asked at the end of their final treatment, an average of 22 days later, about their nausea, and only one S complained of feeling more nauseous. A breakdown of frequency of complaints of nausea was 33 percent, 18 percent, and 7 percent for spinal brain and nonirradiated Ss, respectively. The spinal irradiated Ss showed the greatest frequency of complaints for headaches with 28 percent, brain irradiated only 5 percent, and controls 10 percent. The two complaints of headaches for the brain irradiated Ss were at the pre-exposure level, and throughout the course of treatment there were no complaints of headaches. None of the brain irradiated Ss complained of nausea in the beginning or in the middle of course of treatment, but on the last treatment day, five out of eight Ss complained of feeling more nausea, whereas on the post-treatment follow-up only one S complained of nausea. Thus, overall, the results of health questionnaires indicated that most of the complaints that were registered were by the spinal irradiated Ss, which centered around feelings of nausea and headaches, a common side effect of radiation treatment (Kimeldorf and Hunt, 1965).

(I) Attitudes Toward Radiation. In brief, the analysis of the social distance findings indicated that the nonirradiated Ss would maintain significantly ($P < .001$) more social distance from individuals accidentally exposed to radiation from a nuclear reactor than from nonirradiated normal Ss. They voiced apprehension and fear about coming in contact with irradiated individuals because of fear of

contagiousness of radiation. However, in reality, radiation exposure from nuclear reactors can only harm the person exposed. Surprisingly, the results showed that even radiated patients would maintain significantly more interpersonal distance from individuals accidentally exposed to radiation, than from nonirradiated normals ($P < .05$). However, a content analysis of Ss statements indicated less apprehensiveness about approaching individuals accidentally exposed to radiation than the nonirradiated Ss. However, overall, the content analysis indicated that the majority of statements made by radiated and nonirradiated Ss concerning figures accidentally exposed to radiation were self-protective; i. e., concerns about personal danger from contact and questions about radiation effects. A more detailed account of the findings and methodology can be found in an earlier paper (Wolfgang, 1971b).

Cases with the Highest Dose and Greatest Volume of CNS Irradiation.

Two Ss from the brain and two from the spinal irradiated groups were selected for evaluation on the basis of receiving the highest dose and having the greatest volume irradiated as determined by the radiotherapist. In studying the sensitivity of the CNS to irradiation, it has been shown that volume of tissue irradiated, overall duration of irradiation, and the total dose administered must be taken into consideration (Maier, Perry, Saylor, and Sulak, 1969). The biographical data on these four patients can be found in table 1. Because of the small sample, the data was analyzed in terms of overall percentage of change from the baseline; i. e., pre-exposure (trial 1) score versus median of the trials two, three, four, and five. The most extreme radiation case was a 24-year old female who received total CNS radiation with cobalt therapy for a suspected small cell neoplasm, probably medulloblastoma. She showed no performance decrement on measures of conceptual thinking or decision making ability, memory, motor coordination, and muscle strength. Motivation in terms of interest and effort put forth on the test was high. (Category five on five-point scale from one to five.) Systolic BP showed little change from the baseline. However, on diastolic BP there was a drop from the baseline. The greatest drop was 18mm. from baseline reading of 69 to 51 on the final treatment. On the

post-exposure measure, the diastolic BP readings returned to the normal range (67).

On measures indicating Ss emotional state, the scores were very low for anxiety (2.0), depression (3.6), and hostility (3.2). Ss time horizon was long, in that she could see what her life would be like beyond 5 years into the future. On the health questionnaire, there were no complaints registered across all trials.

In comparison to her nonirradiated counterpart, she showed more overall improvement from the baseline; that is, on seven performance variables she showed improvement, on two a slight decrement, and on one no change, whereas the nonirradiated S showed overall improvement on only four variables, a slight performance decrement on four variables, and no performance change on two variables.

Another brain irradiated case was a 45-year old male, ex-sergeant, mailman, who was treated for a lymphoma of the scalp on the left parietal region with orthovoltage (300 KV 4 mm. Cu.); the total tumor dose was 4,000 rads in 28 days with a daily dose of 200 rads to the tumor. The post-exposure measures included a 3-, 6-, and 18-month follow-up for a total of seven trials instead of the customary five. Radiation treatment resulted in a complete regression of the tumor mass.

On measures of cognitive functioning, the S showed no performance decrement on all measures except for visual CI and associate learning. Both the control S and brain irradiated S showed an overall decrement in associate learning. The overall increase in errors in visual CI was due to the Ss inability to reach a solution on a problem on trial four the day of the last radiation treatment. On follow-up trials 3 months and 6 months later, the S's decision-making ability improved as indicated by a sharp drop in errors and achieving a quick solution to the problem.

On motor skills and muscle strength, the patient showed overall improvement comparable to the control S. On cardiovascular measures, the patient showed a decline in systolic BP from 110 mm. at the pre-exposure level to 98 mm. on trial four, but on post-exposure measures systolic BP increased to 103 mm. and 100 after 3 months and 6 months, respectively. There were no changes over trials in diastolic BP, except on the 3-month follow-up where the

patient's BP dropped from a pre-exposure level of 70 mm. to 59 mm. However, on the 6-month follow-up the systolic BP returned to the normal pre-exposure level.

Measures reflecting emotional state revealed that the patient's anxiety, depression, and hostility scores showed an overall increase over the pre-exposure level. The highest scores on all three measures occurred on the 3-month follow-up but were reduced sharply on the 6-month follow-up. It was just prior to the 3-month follow-up interview that the patient said he was told by a physician at another hospital that he may have another tumor forming. The patient also registered many complaints at this time in answering questions on the health questionnaire. He complained that he was sleeping more than usual and woke up weak and frequently felt nauseous while delivering the mail. He also complained of being hungry all the time. On the plus side, his headaches had subsided and were occurring much less frequently than before treatment.

The patient's major complaint was regarding his memory. He felt his memory was poorer because he would quickly forget what he read or said and even delivered the mail on the wrong street but didn't care. The S said his memory problems began shortly after the final radiation treatment (trial four). The patient was given a complete physical and neurological examination on the 3-month follow-up at Walter Reed, and no evidence of a tumor growth was found. On a follow-up interview 6 months later, all the previous symptoms he complained of including his memory problems disappeared, except that he felt he had little resistance and was susceptible to colds. On the battery of tests, he showed no decrease in performance on any of the test measures and showed as much overall positive change from the pre-exposure level as his nonirradiated counterpart.

The patient was invited back 1 year later (1 1/2-year follow-up) and was interviewed and given a partial battery of tests. The overall results showed that his only complaint was that at times when delivering the mail on his route, for a period of a few seconds he could not recognize the street and the environment seemed strange. He also reported his headaches were occurring less frequently. On the tests, he showed little overall change in memory span, motor coordination, muscle strength, motivation, ability in solving CI problems, and

emotional state except for a slight rise in anxiety from the pre-exposure level. His BP, systolic (102) and diastolic (62), remained below his pre-exposure level.

The next S was a 25-year old male, who received 3,175 rads over 21 days on the 2MVP machine to the entire scalp. Although he was not part of the formal sample, this case was included, because the whole scalp was irradiated for lymphoma cutis, and the patient received in the middle of treatment single doses of 300 rads and 600 rads to the entire scalp, on the final treatment. Another reason the S was not included in the final sample was that he received 50 rads instead of sham irradiation on the first treatment, and not all the tests were administered. Thus, there was a total of three trials with no follow-up, because the S was discharged and moved away. Radiation treatment resulted in complete regression of the scalp lesion.

On the visual conceptual task the S showed low error rates across all trials. For digit-span forward and backward, his scores were in the normal range, and he showed only a slight decrement on digits forward from the first exposure to radiation.

On the tests of motor coordination such as the tapping, he showed steady improvement across all trials achieving higher mean tapping rates than the other three groups in the formal sample. On the Pérdue Pegboard, there was a slight improvement in performance. His muscle strength scores showed little change for both hands over trials and compared to other Ss were below average, approximating the females' mean scores. His motivation scores were in the top category (5), showing that he liked the tests and he put forth great effort to succeed. On time horizon, he could not see into the future at all concerning what his life would be like. The scores on the MAACL reflecting his emotional state in the test situation indicated a sharp drop in anxiety over trials (six, two, and one). There was also a drop in the depression scores (eight, five, and four) and consistently low hostility scores.

Next, there was a 24-year old male who received 4,000 rads of cobalt therapy in 28 days for a Teratocarcinoma stage II. On measures of cognitive functioning, motor coordination, and muscle strength, the patient's performance showed overall improvement over the pre-exposure level. The systolic BP showed little change over trials, whereas the diastolic BP showed an increase over the baseline.

The biggest change in diastolic BP was from a pre-exposure level of 56 mm. to 66mm. at the final treatment. On the follow-up, the BP returned to its pre-exposure level. S's motivation to perform was high and showed no change from the pre-exposure level. The S's overall emotional state fluctuated little from the baseline on anxiety, depression, and hostility.

On questions concerning health in the pre-exposure interview, the patient registered no complaints. On the first day of treatment, the patient said he was sleeping more, eating and drinking less, and felt more nauseous. He attributed these symptoms to the biopsy he had previously and said he was in pain from the operation. In the middle of treatment (trial 3), his only complaint was feeling nauseous and eating less than usual. On the day of the final irradiation treatment, he said he felt he was returning to normal but complained of having more headaches than usual. Finally, on the follow-up interview he continued to complain only of headaches.

In comparison to his nonirradiated counterpart, the patient showed on 10 measures, overall improvement on eight, a slight decrement on two, and no change in performance on one measure. In contrast, the nonirradiated control showed improvement on six measures, a slight decrement on three, and no change on one measure.

The last case to be discussed was a 19-year old male who was treated with 4,000 rads of cobalt therapy with a daily dose of 200 rads for a teratocarcinoma of the right testis. This patient solved the visual (2) and tactile (2.5) conceptual tasks with very few errors and showed a reduction in decision time on both tests over trials. The S's memory span for digits was seven across all trials which is within the normal range. On associate learning, the patient showed a decrement from the pre-exposure level. This decrement was due to poor performance on the first two trials on the task; on the third trial, the patient earned a perfect memory score in associate learning. In comparison to his nonirradiated control, the patient earned higher scores across all trials in associate learning. Improvement over the pre-exposure level was shown in motor skills and muscle strength. There was a drop in systolic BP from 115 mm. on the pre-exposure trial to 103 mm. on the final treatment and a further drop to 97 mm. on the follow-up trial. In contrast, diastolic BP showed a small general increase over

radiation trials and then returned to the pre-exposure BP level on the follow-up trial. The patient's motivation was sufficiently high on both interest and effort put forth on the tests (category 4). The S's emotional state in the test situations showed an increase in anxiety scores over the pre-exposure level (4) on trial 2 (10) and 3 (10) but showed a sharp decrease on trial 4 (3) and 5 (4). The depression scores showed the same trend, and hostility showed a continued drop from the pre-exposure level (13) to the follow-up trial (5).

On the health questionnaire, he reported that most of the difficulties occurred on trial 3 (middle of treatment), the day before he had a biopsy. He complained of feeling nauseous. However, on trials 4 and 5 the patient did not report any health problems.

Overall, the patient showed improvement on six measures, no change on three, and a decrement in performance on one measure, whereas the non-irradiated control showed improvement on four measures, a performance decrement on four, and no change in performance on two measures.

DISCUSSION

What did the results indicate? The results indicated that relatively young Ss receiving CNS irradiation involving the spinal cord or brain for extracranial neoplasms, but otherwise healthy, showed no overall significant differences from their matched nonirradiated controls on a broad spectrum of behavioral measures, ranging from higher mental functioning and memory to motor coordination and muscle strength. The irradiated areas ranged from specific areas of the brain and spinal cord to the entire CNS with single doses ranging from 50 and 250 rads to 600 rads to the entire brain.

Even when extreme cases from the sample were selected on the basis of those receiving the highest dose and volume of ionizing irradiation, the results showed no apparent performance decrement on the battery of measures when comparisons were made with the Ss pre-exposure level performance or with their nonirradiated controls. In fact, the extreme irradiated cases showed more overall positive increments on a greater number of measures (70 percent) than their nonirradiated controls (52 percent). Thus, overall, the results of the present study suggest that a broad range of behavioral functions were highly resistant to impairment from therapeutic CNS irradiation. There is evidence that irradiated animals actually outperformed their controls on a variety of learning problems, and the results of further studies suggested that superior performance was due to decreased distractibility and narrowing of the span of attention (Furchtgott, 1963). At present, there are no human studies that have been done to test these hypotheses.

There were findings indicating CNS disturbance of Ss receiving ionizing irradiation. For instance, the spinal irradiated Ss reported the greatest frequency of complaints that centered mainly on headaches and nausea. Symptoms of nausea would be expected to occur more frequently with the spinal irradiated Ss, since Ss were irradiated in the area of the abdomen. However, the Ss reported on the post-treatment interviews that the nausea and headaches disappeared. Then too, there was the S who received 4,000 rads to the parietal region of the scalp and complained of memory loss shortly after his final treatment.

However, his memory loss proved to be transitory, in that on the post-treatment interview, the S reported that his problems in remembering disappeared.

Out of a total of 28 independent measures from a test battery that was designed to detect CNS disfunction, only three measures significantly differentiated the three main groups (brain, spinal, and nonirradiated controls) and only on one or two (i.e., blood pressure and emotional state) of these measures could changes be considered radiation-induced. One of the measures dealt with latency of response on a tactile discrimination task. However, the main differences between the groups on latency of response were at the pre-exposure level, where brain irradiated Ss responded slowest. On the final radiation exposure trial, the brain irradiated Ss showed a significant improvement in latency, but the other two groups also showed improvement, and there were no differences between the groups on the final trial (see figure 1). Thus, since all groups improved, it was doubtful that it was ionizing irradiation that improved performance for the brain irradiated Ss.

The results relating to blood pressure indicated that systolic BP showed an overall significant decline over trials, which was mainly attributed to the brain and spinal irradiated Ss. However, the differences between the three groups were not large enough to be statistically significant over trials. The results of diastolic BP were more clear-cut with the brain irradiated Ss showing a progressive decrease in BP from the pre-exposure level, where the other two groups showed little change in BP from the pre-exposure level (see figure 2). In many experiments, CNS irradiation has been found to produce initial damage to exposed blood vessels in the circulatory system and that radiation damage may be delayed (Kimeldorf and Hunt, 1965). Then too, it has been shown that patients receiving therapeutic radiation may develop a hypotensive episode shortly after radiation and then return to their normotensive levels within 1 or 2 hours (Best and Taylor, 1966). Hypotension has been observed in several species of animals; i.e., monkeys, cats, and dogs, during the first few days after irradiation (Kimeldorf and Hunt, 1965).

Although the BP findings were statistically significant, there is some doubt as to their clinical significance when considering that the largest overall mean change in diastolic BP for the brain irradiated Ss was only 8 mm. (see figure 3)

from the pre-exposure level to follow-up. At present, although the clinically accepted definition of normal BP is 120/80 mmHg., there is great controversy as to what cutoff points to use to discriminate normal from abnormal blood pressure as indicated at the Princeton Conference (1960). If the criteria for normal arterial blood pressure is used as suggested in the Princeton Conference; i. e., Normotension is when systolic BP is below 140 mmHg. and diastolic below 90 mm.; i. e., both below, then all of the Ss fall in the normal limits. If the definition of limits of hypotension is used as suggested by the survey of Master, Dublin, and Marks (1950), then the upper limits of diastolic BP of males and females age 30-34 are 60 and 55, respectively. As seen in figure 3, none of the mean scores reach the limits of hypotension. Two brain irradiated cases reached hypotensive limits on specific trials indicating that the hypotensive effect was transitory. In both cases, the Ss had extremely low anxiety and depression scores, which may have accounted for the low diastolic BP readings.

The question arises as to why the brain and not the spinal irradiated Ss showed a significant drop in diastolic BP over trials. One plausible hypothesis was that since the brain irradiated Ss reported feeling low anxiety, depression, and hostility in the test situation, that perhaps this relaxed emotional state may have resulted in relaxation of the baroreceptors around the blood vessels, and thus diastolic BP was reduced. The brain irradiated Ss did show a gradual drop in anxiety over the pre-exposure level. Correlational analyses indicated significant positive correlations between anxiety level and diastolic BP ($r = .50$, $P < .05$) and systolic BP ($r = .55$, $P < .01$), and between depression and diastolic ($r = .44$, $P < .05$) and systolic BP ($r = .45$, $P < .05$), indicating that when anxiety or depression in the test situation decreased, diastolic and systolic BP also decreased.

The overall finding that irradiated Ss reported actually less anxiety, depression, and hostility than the nonirradiated controls was surprising, when considering that the irradiated Ss were confronted with a life-threatening disease, cancer, as well as the stress of being exposed to radiation treatment on a daily basis to various parts of the head and spinal cord for several weeks. In fact, the Ss receiving brain irradiation showed the lowest scores on all three clinical scales of MAACL (anxiety, depression, and hostility) and the controls the highest with the spinal in between.

There are several explanations that could help account for these results. Firstly, the Ss were relatively healthy curable cases and may have felt, that with radiation treatment, progress was being made and their cancer was seemingly under control. In fact, Ss with visible tumor masses, particularly the brain irradiated Ss, could see their masses shrink with radiation treatment and thus feel less anxiety or depression. Then too, Ss were tested almost immediately after receiving radiation treatment and may have felt relieved when the treatment was over, when considering that the experience of radiation treatment is quite stressful and anxiety-producing in itself.

Another plausible hypothesis is that cancer patients have difficulty in expressing hostility and emotions. At a recent conference of the American Cancer Society, it was reported by Solomon (1971) that one of the factors consistently found in reports of personality studies of cancer patients was this relative inability of cancer patients to express their emotions and hostility. Bernhard (1968), in his review of the literature on cancer and emotion, reported that research showed that cancer prone Ss tend to keep their feelings bottled up and have not learned to express their emotions freely and openly. In the present study, the cancer Ss were also given the General form of the MAACL; i. e., Ss were asked to check items relating to how anxious, depressed, or hostile they felt in general; i. e., outside of the test situation, and the results indicated that overall the brain and spinal irradiated Ss showed lower scores on all three scales of the MAACL than the nonirradiated controls. These results would tend to be consistent with past studies reported by Solomon (1971) and Bernhard (1968).

The overall results, concerning attitudes toward radiation, indicated that Ss fear of radiation was generalized to a simulated interpersonal situation and resulted in their keeping greater social distance from an individual accidentally exposed to radiation by a nuclear reactor than a normal nonirradiated person. Although no actual harm could come to the Ss, the content analysis of Ss statements about radiation revealed, that whether the Ss received therapeutic radiation or no radiation, they expressed reluctance to come to the aid of a person exposed to radiation. Thus, the results reveal the relative ignorance of Ss about radiation effects, including patients being treated with radiation, thereby

indicating a need for more communication between the radiation therapist and patient about radiation effects.

In looking toward the future of radiation research with humans, the present results point up the need for longitudinal studies to investigate delayed effects of radiation, more research on effects of radiation on physiological variables (e.g., EEG, heart rate, muscle action potential, etc.) to detect the more subtle effects of radiation and the development of behavioral tests with equivalent forms that can be used on several occasions with a minimum of practice effects.

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